FPCH04160022P

AMENDED SHEETS MADE UNDER ARTICLE 34 OF PCT

AMENDED DESCRIPTION
(Pages 24, 29, 30, 31, 32, 69, 75, 76, 89 and 90)
Amended Claims
(Pages 116-135)

meshes silica gel. The filtrate was concentrated in vacuum and recrystallized with a corresponding alcohol. Examples 14 and 15 were treated according to the above procedures.

Example 14
Synthesis of methyl β-carboline-3-carboxylate (9): white solids were obtained, the yield was 66%, mp 308-309℃.

Example 15
Synthesis of ethyl β-carboline-3-carboxylate (10): white solids were obtained, the yield was 77%, mp 230-231℃ (reference: 231-232□).

Example 16

Synthesis of 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (11a)

L- tryptophan (5.10g, 25mmol), H_2SO_4 (0.01M, 30ml) and 40% acetaldehyde (9ml) were added in a 250 ml round-bottom flask, and then stirred and reacted at room temperature for 8 h. After filtration, wash with water and drying, white solids (4.0g, 69%) were obtained.

Example 17

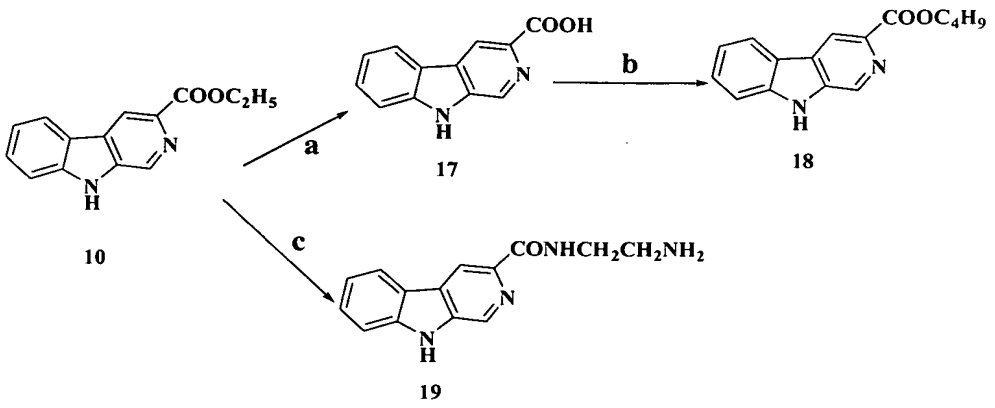
Synthesis of 1-ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (12a)

L- tryptophan (5.10g, 25mmol), water (300ml), H_2SO_4 (0.05M, 30 ml) and propionaldehyde (8ml) were added in a 250 ml round-bottom flask, and then stirred and reacted at room temperature for 24 h. After filtration, wash with water and drying, white solids (4.5g, 74%) were obtained.

Example 18

Synthesis of 1-propyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (13a)

L- tryptophan (5.10g, 25mmol), water (300ml), H_2SO_4 (0.5M, 50 ml), n-butyraldehyde (10ml) and ethanol (100ml) were added in a 250 ml round-bottom flask, and then stirred and reacted at room



a) NaOH, EtOH; HCl b) $SOCl_2$,n-BuOH; c) $CHCl_3$,MeOH

Example 39

Synthesis of β-carboline-3-carboxylic acid (17)

Compound 10 (1.2g, 5mmol), NaOH (0.8g, 20mmol), ethanol (20ml) and H_2O (40ml) were added into a 50 ml round-bottom flask. The mixture was refluxed for 2 h. Ethanol was then evaporated in reduced pressure. The mixture was adjusted to pH with 5M HCl. After cooling with cold water, filtration, wash well with water and recrystallization with ethanol, white solids (0.96g, 90%) were obtained. and mp 307-309℃ (reference: 310℃).

Example 40

Synthesis of butyl β-carboline-3-carboxylate (18)

Compound 17 (2.1g, 10mmol), NaOH (0.8g, 20mmol), n-butanol (100 ml) and thionyl chloride (5ml) were added into a 250 ml round-bottom flask. The mixture was refluxed for 6 h. Excessive n-butanol was then removed in reduced pressure. The residues were dissolved in water followed by the addition of ethyl acetate. While being stirred, the mixture was adjusted to pH 8 with $NaHCO_3$ solution. The organic layer was isolated. The aqueous phase was extracted with

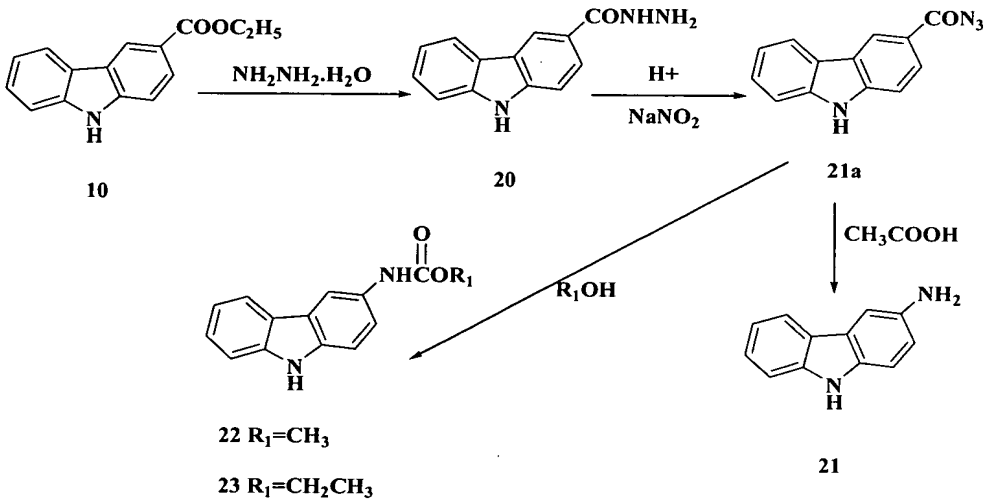
ethyl acetate. The organic phases were combined, washed with water and brine, dried over anhydrous sodium sulfate, decolorized with activated carbon and concentrated in vacuum. The residues were dissolved in ethyl acetate, and purified by silica gel column chromatography with ethyl acetate as the eluent, the recrystallized with ethyl
ether/petroleum ether (2:5) to afford white needle crystals(1.8g, 67%), and mp 211 -212℃(reference: 210-211℃).

Example 41

Synthesis of 3-ethylamino-β-carboline-3-formamide (19)

Ethylenediamine (24ml, 27mmol) was added into a dry 250 ml three-neck round-bottom flask and heated to 80-90℃. While the mixture was stirred, compound 10 (2.4g, 10mmol) was added dropwise and dissolved in a solution of 40ml chloroform and 30ml methanol for about 1 h. The mixture was refluxed for 10 h, and the solvent was evaporated. A mixed solution of 50ml chloroform and 20ml water was added into the residues. After being stored at 4℃ overnight, light yellow solids were precipitated. After filtration and drying, white needle crystals (0.85g, 30%) were obtained. and mp 233-236℃ (reference: 234-237℃, 25%).

Synthetic route III



Example 42

Synthesis of β-carboline-3-carbohydrazine (20)

Ethyl β-carboline-3-carboxylate (10) (2.4 g, 10 mmol) was dissolved in ethanol (50 ml) followed by adding 85% hydrazine hydrate (15 ml). The mixture was refluxed for 6 h and concentrated to 30 ml in reduced
pressure. After cooling, filtration, wash with ethanol, and natural drying in the air, white solids were obtained (2.0g, 80%), Samples for analysis could be recrystallized with 90% ethanol to form white flaring crystals, and mp 289-290℃ (reference: 289-291℃).

Example 43

Synthesis of 3-(azidocarbonyl)-β-carboline (21a)

Concentrated HCl (1.0ml) was added dropwise into a mixed suspension formed from compound 20 (2.0g, 2.9mmol) and water (50 ml). The light yellow solution was cooled in an ice bath to 0℃, and then an aqueous solution (10ml) of nitrous acid (0.2g, 2.9mmol) was added dropwise to react with the light yellow solution at 0℃ for 30 minutes. The mixed reaction solution was then alkalified with a saturated $NaHCO_3$ solution. Solids were collected by filtration, washed by water and vacuumly dried to afford light yellow solids (0.51g, 77%). Said solids were apt to be decomposed, and further purification was not necessary and used directly for the next steps.

Example 44

Synthesis of 3-amino-β-carboline (21)

Compound 21a (0.6g, 2.5mmol) was dissolved in a solution of 30 ml water/glacial acetic acid (1: 1). The mixture was refluxed for 1h. Accompanied with the formation of carbon dioxide gas, the raw materials was gradually disappeared. Then the solvent was evaporated in reduced pressure. The solid residues were recrystallized by ethyl acetate and then filtered to obtain yellow sheet-like crystals (0.35g, 77%), and mp 288-290℃ (reference: 289 to 291℃).

Example 45

Synthesis of 3-[(methoxycarbonyl)amino]-β-carboline (22)

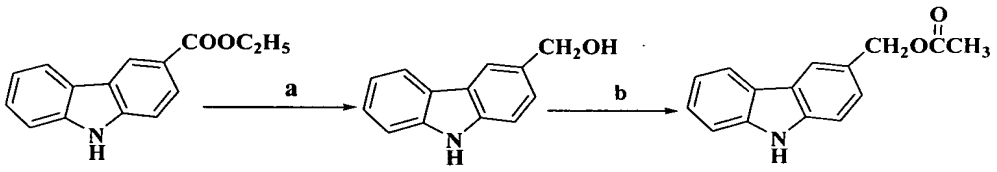
Compound 21a (0.2g, 0.84mmol) was dissolved in methanol (50ml). The mixture was refluxed for 10 h. The reaction mixtrue was cooled, concentrated to 40 ml in vacuum, recrystallized and filtered to obtain white solids (0.12g, 60%). Samples for analysis could be recrystallized with ethanol, and mp 180-182℃, and then decomposed at 230℃.

Example 46

Synthesis of 3-[(ethoxycarbonyl)amino]-β-carboline (23)

Compound 21a (0.2g, 0.84mmol) was dissolved in ethanol (50ml). The mixture was refluxed for 10 h. The reaction liquid was cooled and concentrated to 40 ml in vacuum. After recrystallization and filtration, white solids (0.12g, 60%) were obtained. Samples for analysis could be recrystallized with ethanol, and mp 222-224℃.

Synthetic route IV



10 24 25

a) $LiBH_4$, THF; b) HAc

Example 47

Synthesis of 3-hydroxymethyl-β-carboline (24)

Compound 10 (7.0g, 31mmol) was dissolved in anhydrous THF (900 ml) followed by the addition of $LiBH_4$ (3.4g, 155mmol). The mixture was stirred at room temperature for 9 h and then cooled. Water (100ml) was added into the mixture and stirred overnight. Then the solvent was removed in reduced pressure. With the addition of water (500ml), extraction was conducted with dichloromethane (1 L) and then with ethyl acetate. The organic phases were combined, concentrated in vacuum and purified by silica gel column chromatography with ethyl acetate/methane (3: 1) as the eluent to afford white solids (5.0 g, 82%), and mp 228-230℃ (reference: 225-228℃).

Example 48

Synthesis of 3-acetylmethoxy-β-carboline (25)

Compound 24 (1.98g, 10mmol) was mixed with acetic acid (50ml). The mixture was refluxed for 2 h. The solvent was removed in

ml) followed by the addition of selenium dioxide (20g, 0.2mol). The mixture was refluxed for 12 h. The glacial acetic acid was removed I . 1M NaOH solution (200ml) was added into the residues, then the mixture was extracted with ethyl acetate. The organic phases were combined, washed by 1M NaOH solution, water and brine, dried, decolorized with activated carbon, filtered, evaporated and recrystallized with ethyl acetate to afford white solids (10.0g, 60%), and mp 197-198℃ (reference:198 to 200℃).

Example 111

General procedure for the preparation of 9-substituted β-carboline

β-carboline 80 (1.68 g, 10 mmol) was mixed with DMF (50ml) followed by the addition of alkyl halide or aromatics halide (50mmol). The mixture was stirred at room temperature for 5 h. TLC track measurement was conducted. After the reaction was finished, cold water was poured into the reaction mixture, and then extracted with ethyl acetate. The organic phases were combined, washed by water and brine, dried, decolorized with activated carbon, filtered and evaporated. The residues were purified by silica gel column chromatography with petroleum ether/acetone (2: 1) as the eluent.. The collected liquid was concentrated and recrystallized with ethyl acetate. Examples 112 to 115 were all treated according to the above procedures.

Example 112

Synthesis of 9-methyl-β-carboline (81): Afforded white needle solids (1.4g, 77%), and mp 108-109℃.

sodium sulfate and then concentrated to afford yellow solids. The solids were recrystallized with anhydrous ethanol to afford yellow solids (1.1g, 63%), mp > 270℃.

Example 120

Synthesis of 2,9-dibenzyl-β-carbolinium bromate (89)

Compound 80 (0.84g, 5mmol) was mixed with DMF (30ml) and 60% NaH (0.3g, 15mmol). The mixture was stirred and reacted at room temperature for 10 minutes followed by the addition of benzyl bromide (50mmol). The mixture was stirred and reacted at 50 to 60℃ for 5 h. The reaction mixture was poured into 75ml cold water and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate and then concentrated to afford light yellow solids. The solids were recrystallized with anhydrous ethanol to afford yellow solids (1.8g, 76%), mp > 270℃.

Physico-chemical constants, TLC and spectra analyses of 2,9-disubstituted β-carboline derivatives

Table 21 physico-chemical data of 2,9-disubstituted β-carboline derivatives

Compd	Formula	FW	Yield (%)	Appearance	Solubility	Mp (□)
85	$C_{28}H_{25}N_2IO_2$	548	84	gold solids	soluble in alcohols, DMSO and water	>270
86	$C_{28}H_{25}N_2BrO_2$	501	72	gold solids	soluble in alcohols, DMSO and water	>270
87	$C_{13}H_{13}BrN_2$	277	73	light yellow solids	soluble in methanol, DMSO and water	>270
88	$C_{15}H_{17}BrN_2$	305	63	light yellow solids	soluble in methanol, DMSO and water	>270
89	$C_{25}H_{21}BrN_2$	429	76	light yellow solids	soluble in methanol, DMSO and water	>270

Table 22 FAB-MS, IR and UV data of 2,9-disubstituted β-carboline derivatives

Comp	Formula	FAB-MS m/e(M+1)	IR (KBr, cm^{-1})	$UV_{\lambda max}$ (nm)
85	$C_{28}H_{25}N_2IO_2$	421	ND	ND
86	$C_{28}H_{25}N_2BrO_2$	421	3421,2976,1726,1630, 1517,1457,1367,1304, 1257,1096,1006	397,317,284, 243
87	$C_{13}H_{13}BrN_2$	197	3447,2985,1807,1642, 1517,1467,1376,1335, 1262,1153	390,309,261,257, 220,210
88	$C_{15}H_{17}BrN_2$	225	3437,2977,1815,1639, 1509,1458,1335,1243, 1158,1083	389,310,261, 257, 220, 210
89	$C_{25}H_{21}BrN_2$	349	3409,2982,2935,1644, 1511,1453,1337,1211, 1134	390, 313, 262, 235, 205

Table 23 ^{1}H-NMR data of 2,9-disubstituted β-carboline derivatives

Comp.	^{1}H-NMR(δ, DMSO-d_6)
86	9.88(1H,s,H-4),9.30(1H,s,H-1),8.55-8.57(1H,d,J=7.5Hz,H-8),7.87-7.92(2H,m,H-5, H-6),7.55-7.59(1H,m,H-7),7.20-7.36(1OH,m,Ar-H),6.39(2H,s,$^+$N-CH_2-Ar),5.98(2H,s,NCH_2-Ar),4.44-4.48(2H,m,OCH_2CH_3),1.34-1.37(3H,m,OCH_2CH_3)
87	9.42(1H,s,H-4),8.66-8.67(1H,d,J=6.5Hz,H-1),8.51-8.52(1H,d,J=6.0Hz,H-8),8.43-8.45(1H,d,J=8Hz,H-3),7.83-7.91(2H,m,H-5,H-6),7.50-7.53(1H,m,H-7),4.57(3H,m, $^+NCH_3$),4.13(3H,m,NCH_3)
88	9.61(1H,s, H-4),8.68-8.69(1H,d,J=6.5Hz,H-1),8.61-8.63(1H,d,J=6.5Hz,H-8),8.42-8.44(1H,d,J=8Hz,H-3),7.84-7.89(2H,m,H-5,H-6),7.48-7.51(1H,m,H-7),4.83-4.87(2H,m,$^+NCH_2CH_3$),4.67-4.72(2H,m,NCH_2CH_3),1.75-1.78(3H,m, $^+NCH_2CH_3$),1.51-1.54 (3H,m,NCH_2CH_3)
89	9.57(1H,s, H-4),8.71(2H,s,H-1,H-8),8.42-8.44(1H,d,J=8.5Hz,H-3),7.81-7.82(2H,m, H-5, H-6),7.40-7.50(6H,m,H-7,Ar-H),7.19-7.28(5H,m,Ar-H),5.95(2H,s,N^+CH_2Ar), 5.86(2H,s, NCH_2Ar)

Example 121 Assay of acute toxicities

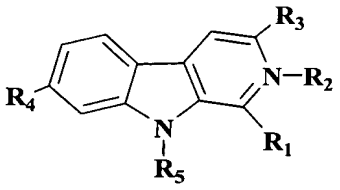
compound 86. As for compound 86, the death peak occurred 2 to 3 days after the medicament was administered. Generally, no obvious abnormal organs were observed after the dead animals were dissected. Survived animals recovered to normal state gradually.

3.2 Results of neurotoxicity and acute toxicity (LD_{50}/MTD)

See table 120-1 to table 120-10 for results of dosage-reaction value and LD_{50} value or MTD value.

For the convenience of comparison, the results of the previous tests on acute toxicity and the results of the present tests are shown in table 34.

Table 34 Results of neurotoxicities and the acute toxicities **(LD_{50}/MTD)** of β-carboline derivatives



Compd	R_1	R_2	R_3	R_4	R_5	LD_{50}	MTD	Neurotoxic
1*	CH_3	H	H	CH_3O	H	59.00	—	++
2*	CH_3	H	H	CH_3O	CH_3	28.92	—	++
3*	CH_3	H	H	CH_3O	C_2H_5	24.25	—	++
4*	CH_3	H	H	CH_3O	n-C_4H_9	26.45	—	++
6*	CH_3	H	H	CH_3O	$CH_2C_6H_5$	147.82	—	++
11	CH_3	H	$CO_2C_2H_5$	H	H	183.47	—	_
16	C_6H_5-p-OH	H	CO_2CH_3	H	H	—	240	_

17*	H	H	COOH	H	H	135.22	–	–
26*	H	H	$CO_2C_2H_5$	H	CH_3	70.61	–	+
27*	H	H	$CO_2C_2H_5$	H	C_2H_5	95.06	–	+
33	H	H	$CO_2C_2H_5$	H	$CH_2C_6H_5$	240.38	–	–
36	H	H	COOH	H	n-C_4H_9	–	>300	–
37	H	H	COOH	H	$CH_2C_6H_5$	163.48	–	–
42	H	H	CH_2OH	H	$CH_2C_6H_5$	247.13	–	–
48	H	H	COOH	H	$(CH_2)_3C_6H_5$	219.19	–	–
55	H	H	$NHCO_2C_2H_5$	H	$CH_2C_6H_5$	–	240	–
84	H	H	H	H	$CH_2C_6H_5$	–	240	–
86	H	$CH_2C_6H_5$	$CO_2C_2H_5$	H	$CH_2C_6H_5$	65.7	–	–

Note: nervous toxicity is represented by "+" and "-", wherein "++" represents significant nervous toxicity, "+" represents nervous toxicity, and "-" represents no nervous toxicity.

Example 122 *In vitro* cytotoxicy assays

1. Materials and method

1.1 Materials

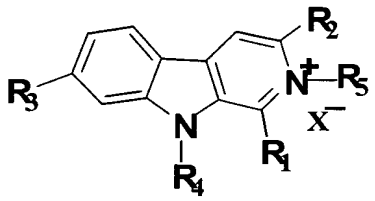
(1) Reagents

RPMI1640 culture medium (GIBCO, U.S.), MTT (Sigma, U.S.), Fetal Bovine Serum (GIBCO or Hyclone, U.S.), HEPES (Sigma, U.S.), trypsin operating fluid (0.125% trypsin, Sigma, 0.01%EDTA, dissolved in D-Hanks solution), DMSO (Sigma, U.S.), cell freezing solution (90%FBS + 10%DMSO), D-Hanks balanced salt solution (i.e. Hanks solution free of calcium and magnesium ions: 8g NaCl, 0.4g KCl, 0.06g $Na_2HPO_4.2H_2O$, 0.06g $KH_2PO_4.2H_2O$, 0.35g $NaHCO_3$ were dissolved in tri-distilled water with no phenol red), PBS(8g NaCl, 0.2g KCl, 1.56g $Na_2HPO_4.2H_2O$, 0.2g $KH_2PO_4.2H_2O$ were dissolved in tri-distilled water) were used.

Chemicals: 88 compounds synthesized as described in the second part of the description and harmine of formula **1**.

The Claims

1. A compound of the following formula (I)



wherein

R_1 is selected from the group consisting of hydrogen, linear or branched C_{1-6} alkyl, C_{6-10} arylalkyl, mono- or multi-substituted C_{6-10} arylalkyl, heterocyclic group and alkenyl, wherein the substituents are defined to be halogen, C_{1-4} linear or branched alkyl, C_{1-4} linear or branched alkoxy, nitro, amino, hydroxyl and carboxyl;

R_2 is selected from the group consisting of hydrogen, carboxyl, ester group, carboxylate, acylamino, acyl halide group, linear or branched C_{1-6} alkoxycarbonyl, C_{6-10} arylalkoxycarbonyl, mono- or multi- C_{6-10} arylalkoxycarbonyl, and or heterocyclic oxycarbonyl, wherein the substituents are defined as above;

R_3 is selected from the group consisting of hydrogen, hydroxyl, linear or branched C_{1-6} alkoxy, carboxylic esters, carboxylic salts, C_{6-10} arylalkoxy, and heterocyclic oxy group;

R_4 is selected from the group consisting of hydrogen, linear or branched C_{1-6} alkyl, hydroxyl- linear or branched C_{1-6} alkyl, C_{6-10} arylalkyl, mono- or multi-substituted C_{6-10} arylalkyl, and heterocyclic group, wherein the substituents are defined as above;

R_5 is selected from the group consisting of hydrogen, C_{1-6} linear or branched alkyl, C_{6-10} arylalkyl, mono- or multi-

substituted C_{6-10} arylalkyl, wherein the substituents are defined as above;

X is selected from the group consisting of pharmacologically acceptable organic or inorganic acid radical, wherein the organic acids include Lewis acid,

or R_5 and X do not co-exist; and

R_1, R_2, R_3, R_4 and R_5 do not represent hydrogen at the same time, and

when R_2, R_4 and R_5 are hydrogen, R_1 does not represent methyl and R_3 does not represent methoxy;

when R_1 is methyl, R_2, R_3, R_4 and R_5 do not represent hydrogen at the same time;

when R_1 is methyl, R_2 and R_5 are hydrogen, and R_3 is methoxy, R_4 is not methyl, ethyl or butyl;

when R_1, R_3 R_4 and R_5 are hydrogen, R_2 is not C_{1-4} linear or branched alkoxycarbonyl;

when R_1 is methyl, R_2 is hydrogen, and R_3 is linear or branched alkoxy, R_4 and R_5 do not represent hydrogen at the same time,

when R_1, R_3 and R_4 are hydrogen, R_2 is ethoxycarbonyl and X is trifluoromethylsilyl, R_5 is not *n*-propyl, allyl, or ortho-, meta-, or *p*-fluorobenzyl; and at the same time

the following compounds are excluded:

Ethyl 1-methyl-β-carboline-3-carboxylate,

Methyl-1-phenyl-β-carboline-3-carboxylate,

Methyl 1-(4-methoxy) phenyl-β-carboline-3-carboxylate,

β-Carboline-3-carboxylic acid,

3-Hydroxymethyl-β-carboline,

3-Amino-β-carboline,

3-[(Methoxycarbonyl)amino]- β-carboline,

3-[(Ethoxycarbonyl)amino]-β-carboline,
Ethyl 9-methyl-β-carboline-3-carboxylate,

Ethyl 1,9-dimethyl-β-carboline-3-carboxylate,

Ethyl 9-benzyl-1-methyl-β-carboline-3-carboxylate, and

9-Methyl-β-carboline.

2. The compound according to claim 1, characterized in that R_1 is selected from the group consisting of hydrogen, C_{1-6} linear or branched alkyl, C_{6-10} aryl-C_{0-6} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{0-6} linear or branched alkyl.

3. The compound according to claim 2, characterized in that R_1 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, C_{6-10} aryl-C_{0-4} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{0-4} linear or branched alkyl.

4. The compound according to claim 3, characterized in that R_1 is selected from the group consisting of hydrogen, C_{1-2} alkyl, phenyl-C_{0-4} linear or branched alkyl, mono- or multi-substituted phenyl-C_{0-4} linear or branched alkyl.

5. The compound according to claim 4, characterized in that R_1 is selected from hydrogen, methyl, phenyl, and mono- or multi-substituted phenyl.

6. The compound according to claim 5, characterized in that R_1 is selected from hydrogen or methyl.

7. The compound according to claim 5, characterized in that R_1 is hydrogen.

8. The compound according to claim 5, characterized in that

R_1 is methyl.

9. The compound according to claim 1, characterized in that R_2 is selected from the group consisting of hydrogen, carboxylic acid, carboxylic metal salts, C_{1-6} linear or branched alkoxycarbonyl, C_{6-10} aryl-C_{1-6} linear or branched alkoxycarbonyl, mono- or multi- C_{6-10} aryl-C_{1-6} linear or branched alkoxycarbonyl, and when R_2 is a carboxylic metal salt, R_5 and X are not present simultaneously.

10. The compound according to claim 9, characterized in that R_2 is selected from the group consisting of hydrogen, carboxylic acid, carboxylic metal salts, C_{1-4} linear or branched alkoxycarbonyl, phenyl-C_{1-4} alkoxycarbonyl, mono- or multi-phenyl-C_{1-4} alkoxycarbonyl, and when R_2 is a carboxylic metal salt, R_5 and X are not present simultaneously.

11. The compound according to claim 10, characterized in that R_2 is selected from the group consisting of hydrogen, carboxylic acid, carboxylic alkali metal salts, C_{1-2} alkoxycarbonyl, benzyloxycarbonyl, wherein the alkali metals refer to lithium, sodium, potassium, rubidium and cesium.

12. The compound according to claim 11, characterized in that R_2 is selected from the group consisting of hydrogen, carboxylic acid, sodium or potassium carboxylate, and ethoxycarbonyl.

13. The compound according to claim 12, characterized in that R_2 is hydrogen.

14. The compound according to claim 12, characterized in that R_2 is carboxylic acid.

15. The compound according to claim 12, characterized in that R_2 is sodium carboxylate.

16. The compound according to claim 12, characterized in that R_2 is ethoxycarbonyl.

17. The compound according to claim 1, characterized in that R_3 is selected from the group consisting of hydrogen, hydroxyl, C_{1-6} linear or branched alkoxy, C_{6-10} aryl-C_{1-6} linear or

branched alkoxy, and heterocyclic oxy group.

18. The compound according to claim 17, characterized in that R_3 is selected from the group of hydrogen, hydroxyl, and C_{1-4} linear or branched alkoxy.

19. The compound according to claim 18, characterized in that R_3 is selected from the group consisting of hydrogen and C_{1-2} alkoxy.

20. The compound according to claim 19, characterized in that R_3 is hydrogen.

21. The compound according to claim 1, characterized in that R_4 is selected from the group consisting of hydrogen, C_{1-6} linear or branched alkyl, hydroxyl- C_{1-6} linear or branched alkyl, C_{6-10} aryl-C_{1-6} linear or branched alkyl, and mono- or multi-substituted C_{6-10} aryl-C_{1-6} linear or branched alkyl.

22. The compound according to claim 21, characterized in that R_4 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, hydroxyl-C_{1-4} linear or branched alkyl, C_{6-10} aryl-C_{1-4} linear or branched alkyl, and mono- or multi-substituted C_{6-10} aryl-C_{1-4} linear or branched alkyl.

23. The compound according to claim 22, characterized in that R_4 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, hydroxyl-C_{1-2} alkyl, phenyl-C_{1-4} linear or branched alkyl, and mono- or multi-substituted phenyl-(C_{1-4}) linear or branched alkyl.

24. The compound according to claim 23, characterized in that R_4 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, phenyl-C_{1-2} alkyl, and mono- or multi-substituted phenyl-C_{1-2} alkyl.

25. The compound according to claim 24, characterized in that R_4 is selected from the group consisting of hydrogen, ethyl, butyl, benzyl and pentafluorobenzyl.

26. The compound according to claim 25, characterized in that R_4 is butyl.

27. The compound according to claim 25, characterized in that R_4 is benzyl.

28. The compound according to claim 25, characterized in that R_4 is pentafluorobenzyl.

29. The compound according to claim 1, characterized in that R_5 is selected from the group consisting of hydrogen, linear or branched C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{1-6} linear or branched alkyl, and heterocyclic ring; or R_5 is not present.

30. The compound according to claim 29, characterized in that R_5 is selected from the group consisting of hydrogen, linear or branched C_{1-4} alkyl, C_{6-10} aryl-C_{1-4} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{1-4} linear or branched alkyl, and heterocyclic ring; or R_5 is not present.

31. The compound according to claim 30, characterized in that R_5 is selected from the group consisting of hydrogen, linear or branched C_{2-3} alkyl, phenyl-C_{1-4} linear or branched alkyl, mono- or multi-substituted phenyl-C_{1-4} linear or branched alkyl; or R_5 is not present.

32. The compound according to claim 31, characterized in that R_5 is selected from the group consisting of hydrogen, phenyl-C_{1-2} alkyl, mono- or multi-substituted phenyl-C_{1-2} alkyl; or R_5 is not present.

33. The compound according to claim 32, characterized in that R_5 is selected from the group consisting of hydrogen, benzyl, mono- or multi-halogenated benzyl; or R_5 is not present.

34. The compound according to claim 33, characterized in that R_5 is selected from the group consisting of hydrogen, benzyl, pentafluorobenzyl; or R_5 is not present

35. The compound according to claim 34, characterized in that R_5 is hydrogen.

36. The compound according to claim 34, characterized in that R_5 is
benzyl.

37. The compound according to claim 1, characterized in that X is selected from the group consisting of halogen, nitroxyl, sulfuric acid group, sulfonic acid group, and phosphate group; or X is not present.

38. The compound according to claim 37, characterized in that X is halogen; or X is not present.

39. The compound according to claim 38, characterized in that X is selected from the group consisting of chloro, bromine or iodine.

40. The compound according to claim 38, characterized in that X is chloro.

41. The compound according to claim 38, characterized in that X is bromine.

42. The compound according to claim 38, characterized in that X is iodine.

43. The compound according to claim 1, characterized in that R_1 is selected from the group consisting of hydrogen, C_{1-6} linear or branched alkyl, C_{6-10} aryl-C_{0-6} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{0-6} linear or branched alkyl; R_2 is selected from the group consisting of hydrogen, carboxylic acid group, carboxylates, C_{1-6} linear or branched alkoxycarbonyl, C_{6-10} aryl-C_{1-6} linear or branched alkoxycarbonyl, mono- or multi- C_{6-10} aryl-C_{1-6} linear or branched alkoxycarbonyl; R_3 is selected from the group consisting of hydrogen, hydroxyl, C_{1-6} linear or branched alkoxy, C_{6-10} aryl-C_{1-6} linear or branched alkoxy; R_4 is selected from the group consisting of hydrogen, C_{1-6} linear or branched alkyl, hydroxyl- C_{1-6} linear or branched alkyl, C_{6-10} aryl-C_{1-6} linear or branched alkyl, and mono- or multi-substituted C_{6-10} aryl-C_{1-6} linear or branched alkyl; R_5 is selected from the group consisting of hydrogen, C_{1-6} linear or branched alkyl, C_{6-10} aryl-C_{1-6} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{1-6} linear or branched alkyl; X is selected from the group consisting of halogen, sulfonic acid group, sulfuric acid group, nitroxyl, and phosphate group; or R_5 and X do not co-exist simultaneously.

44. The compound according to claim 43, characterized in that R_1 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, C_{6-10} aryl-C_{0-4} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{0-4} linear or branched alkyl; R_2 is selected from the group consisting of hydrogen, carboxylic acid group, carboxylic alkali metal salts, C_{1-4} linear or branched alkoxycarbonyl, C_{6-10} aryl-C_{1-4} linear or branched alkoxycarbonyl, mono- or multi- C_{6-10} aryl-C_{1-4} linear or branched alkoxycarbonyl; R_3 is selected from the group consisting of hydrogen, hydroxyl, C_{1-4} linear or branched alkoxy; R_4 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, hydroxyl- C_{1-4} linear or branched alkyl, C_{6-10} aryl-C_{1-4} linear or branched alkyl, and mono- or multi-substituted C_{6-10} aryl-C_{1-4} linear or branched alkyl; R_5 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, C_{6-10} aryl-C_{1-4} linear or branched alkyl, mono- or multi-substituted C_{6-10} aryl-C_{1-4} linear or branched alkyl; X is selected from the group consisting of halogen, sulfuric acid group, sulfonic acid group, nitroxyl; or R_5 and X do not co-exist simultaneously.

45. The compound according to claim 44, characterized in that R_1 is selected from the group consisting of hydrogen, C_{1-2} alkyl, phenyl-C_{0-2} alkyl, mono- or multi-substituted phenyl-C_{0-2} alkyl; R_2 is selected from the group consisting of hydrogen, carboxylic acid group, carboxylic alkali metal salts, C_{1-2} alkoxycarbonyl; R_3 is selected from the group consisting of hydrogen, hydroxyl, and C_{1-2} alkoxy; R_4 is selected from the group consisting of hydrogen, C_{1-4} linear or branched alkyl, phenyl- C_{1-2} alkyl, and mono- or multi-substituted phenyl-C_{1-2} alkyl; R_5 is selected from the group consisting of hydrogen, C_{3-4} linear or branched alkyl, phenyl-C_{1-2} alkyl, mono- or multi-substituted phenyl-C_{1-2} alkyl; X is halogen; or R_5 and X do not co-exist simultaneously.

46. The compound according to claim 45, characterized in that R_1 is selected from the group consisting of hydrogen, methyl, phenyl, mono- or multi-substituted phenyl; R_2 is selected from the group consisting of hydrogen, carboxylic acid group, sodium or potassium carboxylate, and ethoxycarbonyl; R_3 is selected from the group consisting of hydrogen, hydroxyl, and C_{1-2} alkoxy; R_4 is selected from the group consisting of

hydrogen, ethyl, butyl, benzyl, and pentafluorobenzyl; R_5 is selected from the group consisting of hydrogen, linear or branched butyl, benzyl, and pentafluorobenzyl; X is selected from the group consisting of chloro, bromine and iodine; or R_5 and X do not co-exist simultaneously.

47. The compound according to claim 46, wherein R_1 is hydrogen or methyl; R_2 is carboxylic acid group, sodium carboxylate, or ethoxycarbonyl; R_3 is hydrogen; R_4 is butyl or benzyl; R_5 is hydrogen or benzyl; X is chloro or bromine; or R_5 and X do not co-exist simultaneously.

48. The compound according to claim 1, wherein R_1 is hydrogen; R_2 is ethoxycarbonyl; R_3 is hydrogen; R_4 is benzyl; R_5 is hydrogen; and X is chloro.

49. The compound according to claim 1, wherein R_1 is hydrogen; R_2 is ethoxycarbonyl; R_3 is hydrogen; R_4 is benzyl; R_5 and X do not co-exist simultaneously.

50. The compound according to claim 1, wherein R_1 is methyl; R_2 is ethoxycarbonyl; R_3 is hydrogen; R_4 is pentafluorobenzyl; R_5 is hydrogen, and X is chloro.

51. The compound according to claim 1, wherein R_1 is methyl; R_2 is ethoxycarbonyl; R_3 is hydrogen; R_4 is pentafluorobenzyl; and X do not co-exist simultaneously.

52. The compound according to claim 1, wherein R_1 is hydrogen; R_2 is COOH; R_3 is hydrogen; R_4 is n-butyl; R_5 is hydrogen; and X is chloro.

53. The compound according to claim 1, wherein R_1 is hydrogen; R_2 is COOH; R_3 is hydrogen; R_4 is n-butyl; R_5 is hydrogen; and X do not co-exist simultaneously.

54. The compound according to claim 1, wherein R_1 is hydrogen; R_2 is COOM; R_3 is hydrogen; R_4 is n-butyl; R_5 is hydrogen; X do not co-exist simultaneously; wherein M is a metal.

55. The compound according to claim 54, wherein M is an alkali metal.

56. The compound according to claim 55, wherein M is Na or K.

57. The compound according to claim 55, wherein M is Na.

58. The compound according to claim 55, wherein M is K.

59. The compound according to claim 1, wherein R_1 is hydrogen, R_2 is ethoxycarbonyl, R_3 is hydrogen, R_4 is benzyl, R_5 is benzyl and X is bromine.

60. The compound according to claim 1, wherein R_1 is hydrogen, R_2 is hydrogen, R_3 is hydrogen, R_4 is benzyl, R_5 is benzyl and X is bromine.

61. The compound according to claim 1, which is selected from the group consisting of the following compounds or pharmacologically acceptable salts thereof:

9-Hydroxyethyl-7-methoxy-β-carboline;

9-Benzyl-7-methoxy-β-carboline;

9-(2',3',4',5',6'-Pentafluoro)benzyl-7-methoxy-β-carboline;

9-Phenypropyl-7-methoxy-β-carboline;

Ethyl 1-ethyl-β-carboline-3-carboxylate;

Ethyl 1-n-propyl-β-carboline-3-carboxylate;

Methyl 1-(4-hydroxyphenyl)-β-carboline-3-carboxylate;

3-Acetyloxomethyl-β-carboline;

Methyl 9-methyl-β-carboline-3-carboxylate;

Methyl 9-ethyl-β-carboline-3-carboxylate;

Methyl 9-butyl-β-carboline-3-carboxylate;

Methyl 9-benzyl-β-carboline-3- carboxylate;

Ethyl 9-ethyl-β-carboline-3-carboxylate;

Ethyl 9-butyl-β-carboline-3-carboxylate;

Ethyl 9-benzyl-β-carboline-3-carboxylate;

Ethyl 9-(2',3',4',5',6'-pentafluoro)benzyl-β-carboline-3-carboxylate;

Butyl 9-phenylpropyl-β-carboline-3-carboxylate;

Butyl 9-acetophenone-β-carboline-3-carboxylate;

Butyl 9-methyl-β-carboline-3-carboxylate;

Butyl 9-ethyl-β-carboline-3-carboxylate;

Butyl 9-benzyl-β-carboline-3-carboxylate;

Benzyl 9-benzyl-β-carboline-3-carboxylate;

9-Benzyl-3-hydroxymethyl-β-carboline;

9-Benzyl-3-acetyloxomethyl-β-carboline;

3-Carbohydrazide-9-ethyl-β-carboline;

3-Carbohydrazide-9-benzyl-β-carboline;

3-[(Methoxycarbonyl)amino]-9-ethyl-β-carboline;

3-[(Ethoxycarbonyl)amino]-9-ethyl-β-carboline;

3-[(Ethoxycarbonyl)amino]-9-benzyl-β-carboline;

Ethyl 9-ethyl-1-methyl-β-carboline-3-carboxyate;

Ethyl 9-butyl-1-methyl-β-carboline-3-carboxylate;

Ethyl 9-(2',3',4',5',6'-pentafluoro)benzyl-1-methyl-β-carboline-3-carboxylate;

Ethyl 9-phenylpropyl-1-methyl-β-carboline-3-carboxylate;

Ethyl 9-acetophenone-1-methyl-β-carboline-3-carboxylate;

Ethyl 1-propyl-9-methyl-β-carboline-3-carboxylate;

Ethyl 1-propyl-9-ethyl-β-carboline-3-carboxylate;

Ethyl 9-benzyl-1-propyl-β-carboline-3-carboxylate;

Ethyl 9-phenylpropyl-1-propyl-β-carboline-3-carboxylate;

Methyl 1-phenyl-9-methyl-β-carboline-3-carboxylate and

Methyl 1-phenyl-9-ethyl-β-carboline-3-carboxylate.

62. The compound according to claim 61, the pharmacologically acceptable salt thereof being hydrochloride salt.

63. The compound according to claim 1, which is selected from the group consisting of the following compounds or pharmacologically acceptable carboxylates thereof:

9-Methyl-β-carboline-3-carboxylic acid;

9-Ethyl-β-carboline-3-carboxylic acid;

9-Butyl-β-carboline-3-carboxylic acid;

9-Benzyl-β-carboline-3-carboxylic acid;

9-(2',3',4',5',6'-Pentafluoro)benzyl-β-carboline-3-carboxylic acid;

9-Phenypropyl -β-carboline-3-carboxylic acid;

9-Acetophenone-β-carboline-3-carboxylic acid;

9-Methyl-1-methyl-β-carboline-3-carboxylic acid;

9-Ethyl-1-methyl-β-carboline-3-carboxylic acid;

9-Butyl-1-methyl-β-carboline-3-carboxylic acid;

9-Benzyl-1-methyl-β-carboline-3-carboxylic acid;

9-(2',3',4',5',6'-Pentafluoro)benzyl-1-methyl-β-carboline-3-carboxylic acid;

9-Phenylpropyl-1-methyl-β-carboline-3-carboxylic acid;

9-Acetophenone-1-methyl-β-carboline-3-carboxylic acid;

1-Propyl-9-methyl-β-carboline-3-carboxylic acid;

1-Propyl-9-ethyl-β-carboline-3-carboxylic acid;

9-Benzyl-1-propyl-β-carboline-3-carboxylic acid;

9-Phenylpropyl-1-propyl-β-carboline-3-carboxylic acid;

1-Phenyl-9-methyl-β-carboline-3-carboxylic acid and

1-Phenyl-9-ethyl-β-carboline-3-carboxylic acid.

64. The compound according to claim 63, wherein the carboxylate is a carboxylic metal salt.

65. The compound according to claim 64, wherein the metal is an alkali metal.

66. The compound according to claim 65, wherein the alkali metal is Na or K.

67. The compound according to claim 65, wherein the alkali metal is Na.

68. The compound according to claim 65, wherein the alkali metal is K.

69. The compound according to claim 1, which is selected from the group consisting of the following compounds:

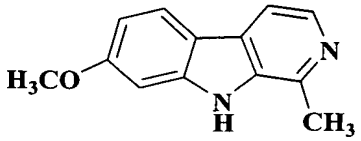
2,9-Dibenzyl-3-ethoxycarbonyl-β-carbolinium iodate;

2,9-Dimethyl-β-carbolinium iodate; and

2,9-Diethyl-β-carbolinium iodate;

70. A method for preparing the compound according to claim 1 comprising the following steps:

1) dissolving harmine (**1**) 1 into an organic solvent or a mixed organic solvent;



1

2) adding 60% NaH and stirring it until there is no bubble formed;

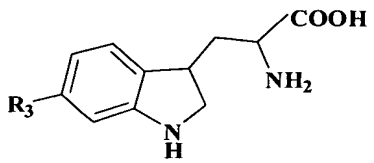
3) adding halogenated alkane;

4) stirring and reacting said mixture at room temperature for 1 to 5 h; and

5) subjecting said mixture to conventional post-treatment and purification to produce 1,7,9-trisubstituted β-carboline alkaloids.

71. A process for preparing the compound according to claim 1 comprising the following steps:

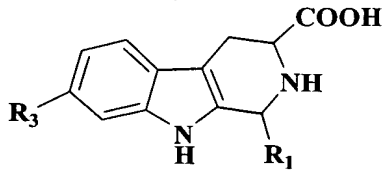
1) using a compound of formula II as the raw material;



(II)

wherein R_3 is as defined above;

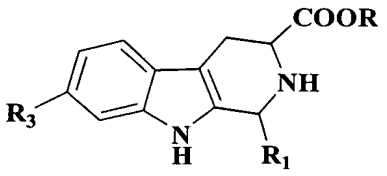
said compound is reacted with an aldehyde (R_1CHO) under the Pictet-Spengler condensation conditions of organic synthesis to form a compound of formula III;



(III)

wherein R_1 and R_3 are as defined above;

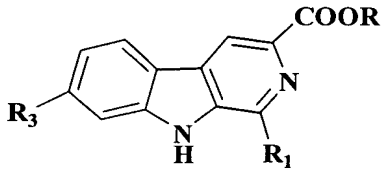
2) the compound of formula III is reacted with an alcohol under conventional esterification conditions of organic synthesis to form a compound of formula IV;



(IV)

wherein R_1 and R_3 are as defined above, and the definition of R is the same as R_1;

3) the compound of formula IV is reacted with a conventional oxidant under conventional oxidation conditions of organic synthesis to form a compound of formula V;

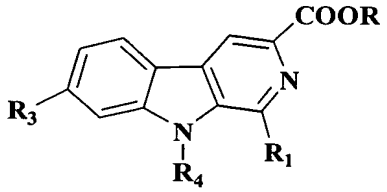


(V)

wherein R_1 and R_3 are as defined above, and the definition of R is the same as R_1;

4) dissolving the compound of formula V in an organic solvent or a mixed organic solvent; adding NaH and stirring it until there is no bubble formed, adding halogenated alkane or aromatics;

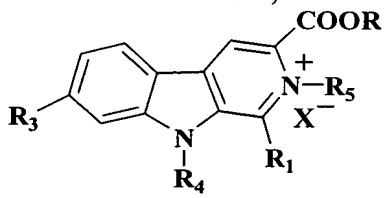
stirring and reacting said mixture at room temperature or by heating for 2 to 5 h; subjecting said mixture to conventional post-treatment to produce a compound of formula VI;



(VI)

wherein R_1, R_3 and R_4 are as defined above, and the definition of R is the same as R_1;

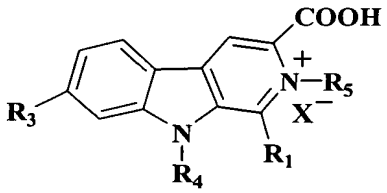
5) the compound of formula VI is reacted with an organic or inorganic acid under conventional salt-forming conditions of organic synthesis to form a compound of formula Ia, i.e. a specific example of the compound of formula I;



(Ia)

wherein R_1, R_3, R_4 R_5 and X are as defined above, and the definition of R is the same as R_1;

6) a hydrolysis reaction is conducted with the compound of formula VI under conventional hydrolysis conditions of organic synthesis followed by acidification by a conventional method to form a compound of formula Ib, i.e. a specific example of the compound of formula I;

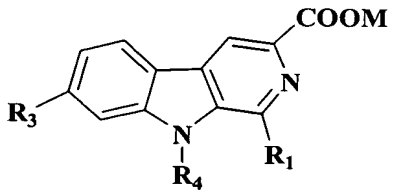


(Ib)

wherein R_1, R_3, R_4 R_5 and X are as defined above, the definition of R is the same as R_1, or R_5 and X are absent simultaneously; and

7) a hydrolysis reaction is conducted with the compound of formula VI under conventional hydrolysis conditions of organic

synthesis followed by acidification by a conventional method to form a compound having a free carboxylic acid group and then to form a compound of formula Ic by forming a salt with a base according to a conventional method, i.e. a specific example of the compound of formula I;

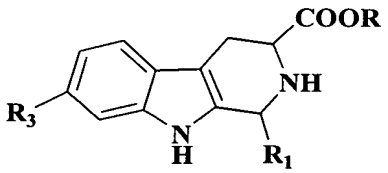


(Ic)

wherein R_1, R_3, and R_4 are as defined above, the definition of R is the same as R_1, and M represents an alkali metal.

72. A process for preparing the compound according to claim 1 comprising the following steps:

1) mixing a compound of formula IV with glacial acetic acid,

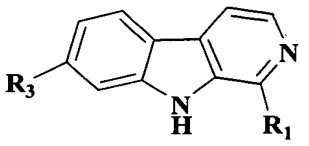


(IV)

2) adding selenium dioxide;

3) refluxing said mixture by heating for 12 h; and

4) subjecting the mixture to conventional post-treatment and purification to produce a compound of formula VII

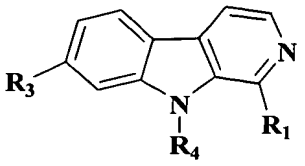


(VII)

wherein R_1 and R_3 are as defined above, and the definition of R is the same as R_1;

5) dissolving the compound of formula VII in an organic solvent or a mixed organic solvent;adding NaH and stirring it until there is

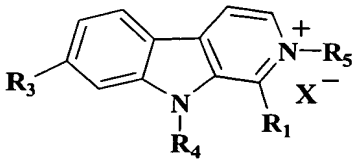
no bubble formed, adding halogenated alkane or aromatics; stirring and reacting said mixture at room temperature or by heating for 2 to 5 h; subjecting said mixture to conventional post-treatment to produce a compound of formula VIII;



(VIII)

wherein R_1, R_3 and R_4 are as defined above, and the definition of R is the same as R_1;

6) the compound of formula VIII is reacted with an organic or inorganic acid under conventional salt-forming conditions of organic synthesis to form a compound of formula Id, i.e. a specific example of the compound of formula I;

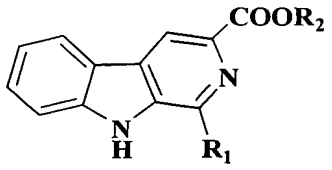


(Id)

wherein R_1, R_3, R_4 R_5 and X are as defined above, and the definition of R is the same as R_1.

73. A process for preparing the compound according to claim 1 comprising the following steps:

1) mixing a compound of the following formula with an organic solvent and 60% NaH;



wherein R_1=H and R_2=C_2H_5;

2) stirring and reacting said mixture at room temperature for 5

minutes;

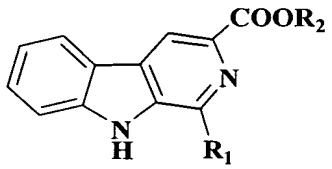
3) adding benzyl iodide;

4) stirring and reacting the mixture at a temperature of from 50 to 70□ for 2 h; and

5) subjecting the mixture to conventional post-treatment and purification to produce 2,9-dibenzyl-3-ethoxycarbonyl-β-carbolinium iodate.

74. A process for preparing the compound according to claim 1 comprising the following steps:

1) mixing a compound of the following formula with an organic solvent and 60% NaH;



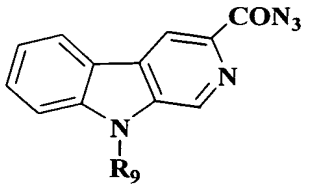
wherein R_1=H and R_2=C_2H_5;

2) adding benzyl bromide;

3) stirring and reacting said mixture at a temperature of from 50 to 70℃ for 5 h; and

4) subjecting the mixture to conventional post-treatment and purification to produce 2,9-dibenzyl-3-ethoxycarbonyl-β-carbolinium bromate.

75. A compound of the following formula (53a-55a):



53a-55a

wherein

R_9 is methyl, ethyl, n-butyl, benzyl, phenylpropyl, mono- or polyhalogenated benzyl or mono- or polyhalogenated phenylpropyl.

76. A pharmaceutical composition for treating tumors, comprising as an active ingredient at least one therapeutically effective amount of a compound of formula I according to any one of claims 1 to 69, alone or combined with one or more pharmaceutically acceptable, inert and non-toxic excipients or carriers.

77. Use of a compound of any one of claims 1 to 69 in the manufacture of a medicament for treating tumors.

78. The use according to claim 77, wherein the tumors refer to alimentary tract tumors, including oral carcinoma, oesophagus cancer, gastric carcinoma, liver cancer and intestinal cancer tumors.

79. The use according to claim 77, wherein the tumors refer to the lung cancer tumors.

80. The use according to claim 77, wherein the tumors refer to the prostatic carcinoma.

81. The use according to claim 77, wherein the tumors refer to the breast cancer tumors.

82. The use according to claim 77, wherein the tumors refer to the ovary cancer tumors.

83. The use according to claim 77, wherein the tumors refer to the cervical carcinoma tumors.

84. The use of a compound of any one of claims 1 to

69 in the manufacture of a medicament combined with phototherapy and radiation therapy for treating tumors.